RESEARCH ARTICLE

Prognostic Significance of 18F-fluorodeoxyglucose Positron Emission Tomography (PET)-based Parameters in Neoadjuvant Chemoradiation Treatment of Esophageal Carcinoma

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Abstract

Aims and Background: The purpose of the research was to study the prognostic value of tumor 18F-FDG PET-based parameters in neoadjuvant chemoradiation for patients with squamous esophageal carcinoma. Methods: Sixty patients received chemoradiation therapy followed by esophagectomy and two 18FDG-PET examinations at pre- and post-radiation therapy. PET-based metabolic-response parameters were calculated based on histopathologic response. Linear regression correlation and Cox proportional hazards models were used to determine prognostic value of all PET-based parameters with reference to overall survival. Results: Sensitivity (88.2%) and specificity (86.5%) of a percentage decrease of SUVmax were better than other PET-based parameters for prediction of histopathologic response. Only percentage decrease of SUVmax and tumor length correlated with overall survival time (linear regression coefficient β: 0.704 and 0.684, *P*<0.05). The Cox proportional hazards model indicated higher hazard ratio (HR=0.897, *P*=0.002) with decrease of SUVmax compared with decrease of tumor size (HR=0.813, *P*=0.009). Conclusion: Decrease of SUVmax and tumor size are significant prognostic factors in chemoradiation of esophageal carcinoma.

Keywords: Esophageal cancer - chemoradiation - positron emission tomography - prognostic factors

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Introduction

Due to different biologic characteristics of tumor for different individual patient, the prognosis varied among patients with esophageal cancer (Heilmann et al., 2008; Cescon et al., 2009). Therefore, the optimal treatment of esophageal cancer should be given according to biologic characteristics of the tumor and other known prognostic factors of the patients. By reflecting individual biologic behavior (DeVita et al., 2008; Javeri et al., 2009b), especially radiosensitivity to X-ray, positron emission tomography (PET)-based parameters were used to guide the treatment of esophageal cancer.

Literatures have reported that PET can be used to stratify patient's prognosis and predict patients' survival in esophageal carcinoma (Choi et al., 2002; Kim et al., 2007; Roedl et al., 2008; Hiyoshi et al., 2009; Klaeser et al., 2009; Schmidt et al., 2009). But used PET-based parameters to stratify prognosis in the literatures varied from different clinical trials, including preradiation SUVmax, postradiation SUVmax, a percentage decrease of SUVmax and a change of PET length. Mostly literatures supported a percentage decrease of SUVmax (%DetaSUVmax) as a prognostic factor (Choi et al., 2002; Kim et al., 2007; Roedl et al., 2008; Hiyoshi et al., 2009; Klaeser et al., 2009; Schmidt et al., 2009). A trial by Schmidt M indicated that FDG-PET predicted histopathological response and survival for locally advanced esophageal cancer (Schmidt et al., 2009). 2-year overall survival rate is 91% for patients with metabolic responses, but only 53% for metabolic nonresponders (*P*=0.007). But Roedl JB thought that a change of PET length was better parameters to predict survival (Roedl et al., 2008). Different PET-based parameters led to more difficulties in the evaluation of those trial results. And which PET-based parameter was an optimal parameter to predict prognosis?

Therefore the prognostic values of 18F-fluorodeoxyglucose PET-based parameters were analyzed in neoadjuvant chemoradiation treatment of esophageal carcinoma in the trial. Another aim of the study was to seek a better PET-based parameter to guide choice of individual radiation treatment of esophageal cancer cases.

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Materials and Methods

Patient Selection

Between January 2005 and October 2008, patients with potentially resectable T2-4N0-1M0 stage squamous esophageal carcinoma were consecutively recruited into this trial at Yantai Yuhuangding Hospital (Yantai, China). All enrolled patients were Han nationality and received neoadjuvant chemoradiation therapy followed by esophagectomy. Resectability before operation was determined based on the evaluation conducted by thoracic surgeons, radiologists, and radiation oncologists. Two 18F-FDG PET/CT scans were performed: one before and one after neoadjuvant chemoradiation. All tumors were staged according to the TNM staging system of the 2002 International Union against Cancer on Cancer staging, based on the histopathologic examination and radiographic images. All patients underwent the following examinations: chest radiography; PET/CT scan; esophageal barium examination; ultrasound examination of the abdomen, including liver, pancreas, kidney, spleen, and retroperitoneal lymph nodes; bone scan; liver and renal function tests; electrocardiography; and blood cell counts. The trial protocol has been approved by institution ethical committee and meets the standards of the Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989, and 1996. All patients gave their informed consent prior to their inclusion in the study.

PET/CT Examination and Assessment of Metabolic Response PET/CT

An 18F-FDG PET/CT scan was performed 1 week before radiation therapy (pre-radiation). Patients didn't receive any treatment before the completion of PET/CT. A radiation plan was subsequently finished for each patient after the first 18F-FDG PET/CT examination. The second FDG-PET/CT scan was performed 1-week post-radiation therapy before surgery (post-radiation).

FDG (GE company, Germany) at a mean dosage of 350 (range: 259-444) MBq was injected intravenously (i.v.) to all patients after ten-hour fasting. A semi-quantitative analysis, using attenuation-corrected images, was performed using the imaging of the primary tumor. The SUVmax was defined as the maximum tracer uptake in the lesion relative to the injected dose and body weight, calculated according to the following formula: SUV=tissue activity concentration (Bq/Kg)/injected dose (Bq)/body weight (Kg). Regions of interest were primary tumor and infiltrated regions. PET-based tumor length was defined as the lesion with SUVmax ≥ 2.4.

Percentage decrease of SUVmax after chemoradiation was calculated with the following equation: a percentage decrease of SUVmax =([pre- SUVmax-post - SUVmax]/(pre-SUVmax) ×100%, where pre-SUVmax and post-SUVmax represent pre- and post-treatment SUVmax respectively; And a percentage decrease of tumor length =([preL-postL]/(preL) ×100%, where preL and postL represent pre- and post-treatment tumor length respectively. Patients were classified as complete metabolic response (CMR, percentage decrease of SUVmax≥75% or decrease of tumor length≥33%), non- complete metabolic response (non-CMR, decrease of SUVmax<75%, or decrease of tumor length<33%), according to data (Choi et al., 2002; Kim et al., 2007; Roedl et al., 2008; Hiyoshi et al., 2009; Klaeser et al., 2009; Schmidt et al., 2009).

Chemoradiation and Esophagectomy

Chemoradiation therapy was given in a concurrent manner. Radiotherapy was delivered by 6-MV X-rays from a linear accelerator (Varian Clinical 23EX; Varian, U.S.A) to the tumor with a dosage of 40-45Gy at 1.8 Gy per fraction with three-dimensional conformal radiotherapy. The chemotherapy regime comprised cisplatin (Qilu Pharmaceutical Co.t, China) given at 40 mg/m^2 on day 1, 2 and then day 22, 23 and continuous infusion of Taxol (Haikou Municipal Pharmaceutical Co.t, China) at 60 mg/m^2 per day for 5 days from days 1 to 5 and days 22 to 26. Esophagectomy and two-field lymph node dissection were performed 4 weeks after chemoradiation therapy by transthoracic approach. For patients with histopathologic positive lymph node or margin, adjuvant radiation was given at the dosage of 20-26Gy/10-13fx.

Analysis and Assessment of Histopathological Response

Pathological examination of the esophageal specimen was performed immediately after the operation. Three designated pathologists were responsible for the histological examination. The esophageal specimen was fixed in 10% neutral formalin overnight, dehydrated in 90% alcohol for 2 hours, embedded into paraffin blocks, and serially sectioned. Each slice was 5 μm thick and stained with hematoxylin and eosin for microscopic examination. Macroscopically normal mucosa close and distant to the tumor and the resection margins were examined. Then microscopic and histological evidence of a tumor bed must be identified, which were histologically characterized by abnormal fibroblastic stroma with no normal esophageal layers and inflammatory cells. Chemoradiation-induced changes histologically included reactive changes such as necrosis, fibrosis, foamy histiocytes, and giant cell reactions. Due to lack of ability to demonstrate any viable and proliferative (nonnecrotic) tumor cells within the specimen, histopathologic responses were determined by dividing the viable residual tumor area by the total tumor area, which was the sum of the areas categorized under the tumor zone according to the published guideline (Becker et al., 2003; Chang et al., 2008; Akutsu et al., 2009; Tong et al., 2010). In case of a diagnostic uncertainty, pathologists reviewed the specimen on a double-headed microscope and immunohistochemical analysis for pancytokeratin was performed. Then a consensus diagnosis was reached.

A 2-tiered classification of Tumor Regression Grading based on the literature (Becker et al., 2003; Chang et al., 2008; Akutsu et al., 2009; Tong et al., 2010) was adopted: complete responder (CR), 0-1% residual tumor; non-complete responder (non-CR), >1% residual tumor. CR was defined as the absence of residual tumor, and fibrosis, mucin lakes, necrotic areas, or keratin flakes extending through the different layers of the esophageal wall. Non-CR was defined as residual cancer cells and/or no signs of tumor regression.

Table 1. Results of Serial FDG-PET Scan and Pathologic Response

	No. of patients (N = 60)	%
Pre-SUVmax (median, range)	8.7(4.8-16.9)	
Post-SUVmax (median, range)	3.7(0.5-10.7)	
Percentage decrease of SUVmax (median, range)	64.3%(14.9%-97.2%)	
Percentage decrease of tumor length (median, range)	24.6% (9.8%-46.1%)	
Post-SUVmax		
Complete metabolic response	17	28.30%
No metabolic response	43	71.70%
Percentage SUVmax decrease		
Complete metabolic response	18	30.00%
No metabolic response	42	70.00%
Percentage PET-length decrease		
Complete response	20	33.30%
No response	40	66.70%

FDG-PET, Fluorodeoxyglucose Positron Emission Tomography; SUV, Standardized Uptake Value

Statistical Analysis

All data were collected prospectively. Linear correlation analysis was used to test the correlation between local control time and overall survival time with PET-based parameters in patients with squamous esophageal carcinoma after chemoradiation therapy. Cox Proportional Hazards Models and multiple factors analysis were used to determine prognostic value of all PET-based parameters with overall survival or disease-free survival. The probability of survival was calculated using the Kaplan–Meier method from the date of operation to the time of death or last date of assessment. Log-rank test was used to compare survival difference among T stage for patients with PET-based CMR or non-CMR. Difference between groups was considered statistically significant if the P value was less than 0.05. The statistical analysis was performed with SPSS 16.0 software for Windows (SPSS, Chicago, IL).

Results

Patient Characteristics

A total of 60 patients (42 men, 18 women; median age, 58 years; range, 39-74 years) were enrolled into this trial. Upper-, middle-, and lower-thoracic esophageal cancer were 15, 30 and 15 patients (all patients: T2, T3 and T4 stage: 17, 27 and 16 patients; N0 and N1 56 and 4 patients; Median length, 7cm range, 4.0-10.5). The follow-up period ranged from 36 to 59 months, with a median of 41 months.

Diagnosis accuracy of metabolic response with pathologic response

Results of serial FDG-PET scan, pathologic response and diagnostic accuracy of PET-based parameters to predict histopathologic response were showed in Table 1 and 2. For PET-based parameters, the sensitivity (88.2%) and specificity (86.5%) of a percentage decrease of SUVmax were the most highest than a percentage decrease of tumor length (81.4% and 80.5%) and post-radiation SUVmax (73.7% and 78.0%) for the prediction of histopathologic response.

Table 2. Diagnostic Accuracy of PET-based Parameters to Predict Histopathologic Response

	PET-based Parameters and Threshold		
	Post-SUVmax(3.0)	Percentage PET-length decrease (33%)	Percentage SUVmax decrease (75%)
Sensitivity	73.70%	81.40%	88.20%
Specificity	78.00%	80.50%	86.50%
Positive Predictive Value	60.90%	75.20%	78.20%
Negative Predictive Value	76.50%	83.80%	86.50%
Positive Likelihood Ratio	3.36	3.48	5
Negative Likelihood Ratio	0.34	0.51	0.55
Accuracy	66.70%	81.30%	86.70%

PET, Positron Emission Tomography

Table 3. Multivariate Cox Proportional Hazards Models Analysis of PET-based Parameters for Overall Survival

PET-based Parameters	HR (95% CI)	*P* value
SUVpre	1.195(0.920, 1.552)	0.183
Lpre	1.136(0.913, 1.413)	0.252
SUVpost	0.740(0.411, 1.332)	0.315
Percentage SUVmax decrease	0.897(0.779, 0.925)	0.002
Percentage PET-length decrease	0.813(0.726, 0.901)	0.009

HR, Hazard Ratio; CI, Confidence Intervals; SUV, Standardized Uptake Value; CMR, complete metabolic response; PMR, Partial Metabolic Response; NMR, non-metabolic response

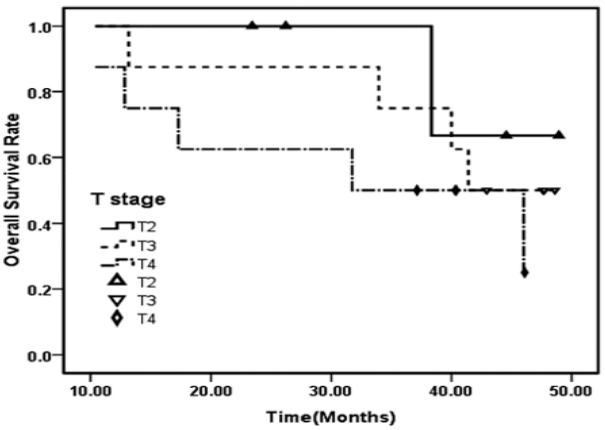

Figure 1. Overall Survival for Patients with CMR in Difference T Stage (P=0.365). CMR, complete metabolic response

Correlation Analysis

By linear correlation analysis, no correlation was found between local control/survival time and post-SUVmax [Linear Regression Coefficient (β)=0.427/0.378, *P*=0.620/0.871]. And percentage SUVmax decrease and PET-length decrease correlated to local control time [β=0.747/0.704, *P*=0.004/0.041] and overall survival time [β=0.705/0.684, *P*=0.013/0.033].

Prognostic Factors

Cox Proportional Hazards Model for overall survival showed that only higher percentage of SUV decrease and tumor length, not pre-radiation SUVmax, pre-radiation length or post-radiation SUVmax, had significant survival advantages (hazard ratio [HR]=0.897 and 0.813, *P*=0.002 and 0.009) (Table 3).

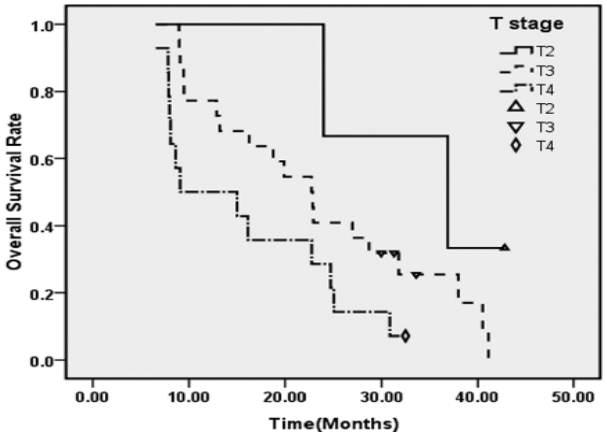

Figure 2. Overall Survival for Patients with Non-CMR in Different T Stage (P=0.030). CMR, complete metabolic response

Influence of T stage on prognostic value of PET-based parameters

For patients with PET-based CMR, T stage would not influence prognostic value of a percentage of SUV decrease (*P*=0.365), which there no significant difference in overall survival (Figure 1). But for patients with PET-based non-CMR, there no significant difference in overall survival (*P*=0.030) (Figure 2).

Discussion

In this trial, percentages decrease of tumor SUVmax and PET length were both significantly independent prognostic factors by the analysis using Cox Proportional Hazards Models (Table 5). And meta-analysis highly supported a percentage decrease of SUVmax as a better prognostic factor (Klaeser et al., 2009). A trial from Roedl JB indicated that a change of PET length was a better prognostic value compared to percentage decrease of SUVmax after chemoradiation (Roedl et al., 2008). But this trial did not support the advantage of a change of PET length compared with %DetaSUVmax in diagnostic accuracy of histopathological response and correlation of survival time for esophageal cancer (Table 3 and 4). Possible cause was that a change of PET length was influenced by more factors, for example the definition of tumor based on SUVmax before or after radiation. Considering more correlation to survival time (Table 4), %DetaSUVmax could favorably be used to clinical treatment in esophageal cancer.

Pre- or postradiation SUVmax did not significantly independent prognostic factors in the trial, but it could stratify patients' prognosis. Suzuki A observed that initial higher SUVmax correlated poorer overall survival (Suzuki et al., 2011). The possible cause was that initial SUVmax obviously correlated T stage. It was found by analysis that the correlation exited (Linear correlation coefficient R=0.686, *P*=0.037) in the trial. Postradiation SUVmax indicated the scale of tumor glucose metabolic rates of tumor residue. Choi NC et al found an inverse correlation between postradiation SUVmax and pathologic tumor response in lung cancer (Choi et al., 2002). Although postradiation SUVmax could be used to stratify the prognosis, it was obviously influenced by radiation inflammatory reaction in prediction survival time (Gillham et al., 2006; Javeri et al., 2009a; Jingu et al., 2010; Suzuki et al., 2011). Most important was that above two parameters did not correlate to survival time (Table 4).

T stage possibly affected prognostic value for PET-based parameters (Gillham et al., 2006; Javeri et al., 2009a; Jingu et al., 2010). For patients with PET-based NMR not CMR, T stage could stratify overall survival for esophageal carcinoma (Figure 1 and 2). These indicated that the role of T stage to patients' survival should be further considered although PET parameters would be used to guide radiotherapy and predict the prognosis.

Our data, which represent results of a small sample and squamous esophageal carcinoma, would not be suitable to gastroesophagael adenocarcinoma. Although a significant survival difference for different histopathological response was detected in survival analysis, the category standard of histopathological response would influence the trial results, for instance <5% residual tumor cells (Akutsu et al., 2009).

In conclusion, Prognostic value for percentage decrease of SUVmax had no difference compared to a change of tumor PET length in PET-based parameters. T stage, as a pretherapeutic factor, could still influence prognostic value of percentage decrease of SUVmax.

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